Difficult-to-Treat Groups and Experimental Approaches

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Abstract and Introduction

Abstract

Purpose of review Novel direct-acting antiviral (DAA) agents are highly effective in the treatment of hepatitis C, achieving unprecedented rates of sustained virological response, a functional cure. However, a significant minority of patients belong to ‘difficult-to-treat’ groups, in which efficacy of DAAs appears less robust. The review article aims to discuss additional treatment strategies which may be employed in these patient cohorts, as well as evidence for the potential role of experimental DAAs.

Recent findings Patients with genotype 3 infection have consistently lower rates of virological clearance following DAA therapy when compared with other genotypes. However, in combination with sofosbuvir, the novel nonstructural protein 5A inhibitor daclatasvir has demonstrated high efficacy in the treatment of noncirrhotic genotype 3 infection. Recent data from phase 2 and 3 clinical studies support the use of currently approved DAA regimens in the treatment of patients with hepatitis C virus and human immunodeficiency virus (HIV) co-infection. Sustained virological response rates in coinfected patients are analogous to those observed in mono-infection, such that HIV infection itself does not pose a barrier to DAA efficacy. In posttransplant populations, DAAs have again shown great potential, with trial data validating use of sofosbuvir/ledipasvir.

Summary Unmet need persists in certain subsets of the hepatitis C patient population. The arrival on scene of novel DAAs is likely to further expand the repertoire of available therapy for these ‘difficult-to-treat’ groups.

Introduction

Across all hepatitis C virus (HCV) genotypes, novel direct-acting antiviral (DAA) agents have demonstrated potential to enhance sustained virological response (SVR) rates above those achieved with interferon (IFN) and ribavirin (RBV) treatment, but significant challenges remain. Most agents are highly active against HCV genotype 1 infection but are less effective for genotype 3, where trials of DAA regimens show suboptimal SVR rates and high frequency of relapse.

Patients with HIV and HCV co-infection and posttransplant populations had lower cure rates with IFN-based therapies. In the United States and Europe, HCV remains the leading indication for liver transplantation,[1,2] and disease recurrence is almost universal after transplantation.[3] Patients with end-stage renal disease represent another group with more limited treatment options.

The advent of novel DAA agents with broader genotypic activity, greater antiviral potency, and higher barriers to resistance present an exciting opportunity to improve outcomes in these patient groups.

Difficult-to-treat Populations in the Direct-acting Antiviral ERA

Genotype 3 Infection

Optimizing DAA treatment for genotype 3 patients is the next major hurdle; genotype 3 infection accounts for approximately 30% of all HCV seen globally[4] and is most strongly correlated with progression to cirrhosis and hepatocellular carcinoma.[5] Historical standard of care for genotype 3 infection was response-guided therapy with pegylated IFN and RBV for up to 48 weeks with SVR rates of around 70%.[6]

All oral therapy is feasible; however, the first regimen sofosbuvir (SOF) and RBV without IFN for 12 weeks produced a disappointing SVR (56%).[7] Extending treatment with SOF/RBV from 12 to 16 weeks in IFN-experienced cohorts with genotype 3 infection resulted in a doubling of SVR12 from 30 to 62%[8] and 24 weeks’ treatment gave SVR12 rates of 94% in genotype 3, treatment-naïve, noncirrhotic patients (n = 92) compared with 60% in treatment-experienced cirrhotic patients.[9]

IFN therapy is not yet dead; it still has a place in genotype 3 therapy. Twelve weeks of SOF/IFN/RBV in genotype 3 infection showed better results, with SVR12 rates of 83% in genotype 3 infection.[10] The benefit of using SOF/pegylated IFN/RBV in genotype 3 patients has recently been confirmed in the phase 3 BOSON study wherein 85% SVR was obtained in a trial.
which contained a significant proportion of previous treatment failure patients and those with advanced fibrotic liver disease.

The ALLY-3 trial of daclatasvir (DAC)/SOF for the treatment of genotype 3 disease showed promising results in both treatment-naive \( (n = 101, \text{SVR 93}) \) and treatment-experienced \( (n = 51, \text{SVR 86}) \) cohorts.\cite{12} Cirrhotic patients fared less well, with overall SVR12 rates of just 63%, which suggests that extending treatment duration to 24 weeks, and/or RBV addition to the SOF/DAC backbone, may be necessary to achieve satisfactory virological clearance in cirrhotic genotype 3 patients.

SOF and the nonstructural protein 5A (NS5A) inhibitor GS-5816 in cirrhotic genotype 3 patients in the absence of RBV achieved SVR rates of 85\cite{13} and 96% with the addition of RBV. A fixed-dose combination tablet containing SOF/GS-5816 is being evaluated with or without RBV in phase 3 trials for the treatment of genotype 3 (ASTRAL-3).

These results are reflected in the European Association for the Study of Liver treatment recommendations for genotype 3, which are SOF and RBV for 24 weeks, or SOF/IFN/RBV for 12 weeks. Combination treatment with SOF with DAC and RBV or ledipasvir (LDV) is also an option.\cite{14}

**Hepatitis C Virus/HIV Coinfection**

Worldwide, approximately 25% of individuals with HIV-1 infection are coinfected with HCV. The introduction of highly active antiretroviral therapy in the 1990s has significantly prolonged life expectancy for patients with HIV. HCV infection is now a common cause of death in this group of patients, who are surviving beyond 20 years from diagnosis.\cite{15}

In patients with HCV genotype 1 and HIV, 12 weeks treatment with SOF/LDV in combination in treatment-naïve, noncirrhotic patients resulted in SVR12 rates of 98%, equivalent to that seen in genotype 1 monoinfection.\cite{16} However, it is important to note that patients with cirrhosis or advanced immunocompromise (CD4+ cell counts of <100 cells/ml) were excluded from this analysis, and hence very little data exist regarding the safety and efficacy of SOF/LDV in those cohorts.

The three-dimensional regimen for HCV genotype 1/HIV coinfection is also effective; in the TURQUOISE-1 trial, patients with HCV genotype 1 and HIV-1 coinfection (CD4+ cell count 200/μl or greater) were randomized to receive 3D + RBV for 12 or 24 weeks giving SVR12 rates of 94% (12 weeks) and 91% (24 weeks).\cite{17}

SOF and DAC in combination for 8 or 12 weeks were studied in the recent ALLY-2 study. Patients coinfected with HCV (genotypes 1–4) and HIV (on antiretroviral medication) achieved SVR12 rates of 97% in both treatment-naïve and experienced groups after 12 weeks of treatment.\cite{18}

These and other clinical studies have confirmed efficacy of DAA-based regimens in the treatment of patients coinfected with HCV and HIV with SVR12 rates similar to those of monoinfected patients. HIV is now not considered a negative predictor of treatment response. Drug interactions remain an issue when antiretroviral treatment is taken concomitantly with DAA agents, and hence treatment options may be more restricted than for monoinfected patients.

**Posttransplant Hepatitis C Virus Populations**

HCV recurrence posttransplantation is universal in preoperatively viraemic patients, which leads to accelerated development of cirrhosis, graft loss, and mortality. IFN-based regimens to treat HCV recurrence are poorly tolerated and have substantially lower response rates than in nontransplant populations. SOF/LDV and RBV have been studied for 12 or 24 weeks in posttransplant HCV recurrence in patients with genotype 1 or 4 disease \( (n = 233) \), including patients with advanced fibrosis and decompensated cirrhosis. SVR12 rates of 97, 96, 84, and 62% were obtained in F0–F3 patients, Child-Pugh A, B, and C cirrhosis, respectively. The majority of patients experienced a reduction in Model for End-Stage Liver Disease scores after successful therapy.\cite{19}

Similar evidence supports the 3D regimen + RBV in genotype 1 patients with posttransplant HCV recurrence, with SVR24 rates of 96%.\cite{20} The efficacy of this regimen in advanced fibrosis or cirrhosis posttransplant remains unclear, as the trial included only patients with F0–F2 fibrosis. Ritonavir-related drug interactions, in particular increased circulating concentrations of calcineurin inhibitors, may influence the uptake of this regimen in posttransplant populations.

SOF/simeprevir (SMV) in combination in the treatment of HCV genotype 1 recurrence postliver transplant showed SVR12 rates of 90%.\cite{21} Addition of RBV did not influence SVR12 rates in this study, although there was a lower response rate in genotype 1a-infected patients with advanced fibrosis (SVR12 71%). There is also the potential for SMV to alter circulating concentrations of cyclosporine and tacrolimus, through its interaction with the hepatic cytochrome P450 system.

Renal failure remains an area where there is little data. SOF is contraindicated in patients with an estimated glomerular
filtration rate less than 30 ml/min, and clinical trials of this and other agents in patients with significant renal disease are ongoing.

New Agents

Grazoprevir/Elbasvir

Grazoprevir (MK-5172) is a novel NS3/4a protease inhibitor developed by Merck, which appears to have high antiviral potency with a high barrier to resistance. The C-WORTHY trial investigated the combination of grazoprevir and elbasvir (an NS5A inhibitor), with or without RBV in treatment-naïve or treatment-experienced genotype 1-infected patients with cirrhosis. SVR12 rates of 97 and 91%, respectively, were seen with no numerical advantage to RBV. These results compare well with SOF and LDV in combination (SVR12 86% in cirrhotic genotype 1 patients) or the 3D/ritonavir regimen (SVR12 82–87% in patients with cirrhosis).

In treatment-naïve cirrhotic and noncirrhotic patients (n = 421) with genotype 1, 4, or 6 infection, grazoprevir/elbasvir yielded SVR12 rates of 92% for genotype 1a infection, 99% for genotype 1b, 100% for genotype 4, and 80% for genotype 6 infection. Of cirrhotic patients (n = 70), SVR12 rates of 97% overall were achieved.

C-SWIFT is evaluating the efficacy of grazoprevir/elbasvir with SOF in treatment-naïve genotype 3 patients (n = 41), with or without cirrhosis for 8 or 12 weeks. Initial data showed 100% SVR12 rates for noncirrhotic patients after 12 weeks of therapy (SVR12 91% after 8 weeks). Among cirrhotic genotype 3 patients, a high SVR12 of 91% was reported.

ABT-493 and ABT-530

ABT-493 (marketed by AbbVie) is a new NS3/4A protease inhibitor, which has shown promising results in vitro, with broad genotypic activity and a high barrier to resistance. In-vitro assessment of antiviral potency and resistance profiles of ABT-493 and a NS5A inhibitor (ABT-530) demonstrated high potency and broad genotypic activity of ABT-493 monotherapy, with particular efficacy against genotype 3a infection (EC50 = 1.6 nM). ABT-493 is entering clinical trial programmes now.

Sofosbuvir, GS-5816, and GS-9857

GS-5816 is an investigational NS5A inhibitor with pan-genotypic activity. In combination with the NS3/4a inhibitor GS-9857 in genotype 1 infection, SVR12 rates were 93 and 87% in treatment-naïve patients, without and with cirrhosis. In patients who had previously failed DAA treatment, SVR12 of 67% was observed. Larger phase 3 trials are ongoing.

Conclusion

The treatment of genotype 3 disease remains an area of challenge, with currently available DAA regimens providing suboptimal responses. IFN continues to have a role in genotype 3 disease, pending the advent of the next generation of drugs. Other previously difficult-to-treat groups, including patients with decompensated cirrhosis, postliver transplantation, other solid organ transplant recipients, renal failure, and HBV or HIV coinfection, have now options for treatment with a much greater chance of cure than in the IFN era.

Sidebar

Key Points

- Treatment of genotype 3 disease, cirrhotic and treatment-experienced patients remains problematic, with currently available DAA agents producing suboptimal response rates.

- Postliver transplant responses are considerably improved with the use of DAAs.

- Efficacy of currently approved DAA regimens is similar in HCV/HIV coinfected cohorts and those with HCV monoinfection.

References


* The multicentre study was the first to report high efficacy and tolerability of SOF/SMV in combination for the treatment of HCV genotype 1 recurrence posttransplantation. Excellent SVR rates were achieved both with and without RBV, except in genotype 1a patients with advanced fibrosis. These results may signal potential for an RBV-free DAA regimen, which can successfully combat genotype 1 recurrence in transplant recipients.

22. Lawitz E, Gane E, Pearlman B, et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. Lancet 2015; 385:1075–1086.


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